PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 111.23F	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043112	International filing date *(day/month/year)* 21.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D471/04 A61K31/437		
Applicant K.U. LEUVEN RESEARCH & DEVELOPMENT		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 20 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	25.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043112

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 4-243	as originally filed
3	filed with telefax on 05.12.2005

Claims, Numbers

1-69	filed with telefax on 05.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-69
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III

For the assessment of the present claims 64-69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 64-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V and VI

Reference is made to the following documents:

D1: EP-A-1 132 381 (CERMOL S.A) 12 September 2001 (2001-09-12)
D2: US-A-5 302 601 (KHANNAL ET AL) 12 April 1994 (1994-04-12)
D3: US-A-4 990 518 (KHANNA ET AL) 5 February 1991 (1991-02-05)
D4: WO 96/12703 A (G.D. SEARLE & CO; KHANNA, ISH, KUMAR; STEALEY, MICHAEL, ALLAN; WEIER,) 2 May 1996 (1996-05-02)
D5: US-A-5 486 525 (SUMMERS, JR. ET AL) 23 January 1996 (1996-01-23)
D6: EP-A-0 076 530 (JANSSEN PHARMACEUTICA N.V) 13 April 1983 (1983-04-13)
D7: US-A-5 585 492 (CHANDRAKUMAR ET AL) 17 December 1996 (1996-12-17)
D8: US-A-5 137 896 (VAN DAELE ET AL) 11 August 1992 (1992-08-11)
D9: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15)

D10: EP-A-0 417 745 (G.D. SEARLE & CO) 20 March 1991 (1991-03-20)

D11: WO 99/27929 A (MERCK & CO., INC; HALCZENKO, WASYL; STUMP, CRAIG, A) 10 June 1999 (1999-06-10)

D12: US-A-5 227 384 (KHANNA ET AL) 13 July 1993 (1993-07-13)

D13: US-A-5 446 032 (WHITTAKER ET AL) 29 August 1995 (1995-08-29)

D14: EP-A-0 344 414 (G.D. SEARLE & CO) 6 December 1989 (1989-12-06)

D15: US-A-5 011 832 (DININNO ET AL) 30 April 1991 (1991-04-30)

D16: GB-A-2 158 440 (FARMITALIA CARLO ERBA S P A) 13 November 1985 (1985-11-13)

D17: RYUICHI ET AL:: "Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent" CHEM. PHARM. BULL, vol. 43, no. 3, 1995, pages 450-460, XP001206481

D18: THOMAS D. PENNING ET AL.: "Synthesis of Imidazopyridines as Potent Inhibitors of Leukotriene A4 Hydrolase" BIOORGANIC AND MEDICINIAL CHEMISTRY LETTERS, vol. 13, 2003, pages 1137-1139, XP002333169

D19: YUTILOV YU M ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" 1989, CAPLUS , XP002265211

D20: G.B. BERLIN, "Ionisation Constants of Heterocyclic Subsatnces, Part VIII, 1,3,5 Triazindenes, Physical, Journal of the Chemical Society[SEction B]: Physical Organic, vol.4 , 1966, pages 285-291

D21: RYUCHI KIYAMA"Synthesis and Evaluation of Novel NonpeptideAngiotensin II Receptor Antagonists": Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent, Chem. Pharm. Bull. 43(3), pages 450-460.

D22: GERHARD CLEVE ET AL., Derivate des Imidazo[4,5-b]- und Imidazo[4,5-c]pyridins., Liebigs Ann. Chem., 747,1971, pages 158-171

D20-D22 were cited in the internationational search report, but are mentioned in the description of the present application.

D9 has a publication date, which is prior to the filing date of the present application. It may be noted that D9 has entered the European phase of examination.

The present claims do not appear to be entitled to the earlier priority date of 22.12.2003, such that D9 is relevant both for the examination of novelty and inventive step.

Novelty

Novelty destroying subject matter

Example 51 of D1 is novelty destroying to the present claim 1.and a number of further claims. (The subject matter of the claims differs from further examples in D1 from through the fact that R^3 does not include saturated heterocycles).

5-[(4-fluorophenyl)methyl]-N-methyl-5H [4,5-c]pyridine-2-amine disclosed on page 75, lines 26-27 of D6 and column 43, lines 38 and 39 of D8 is still novelty destroying to the present claim 1 and a number of further claims.

The subject matter of the present claims overlaps with that of D9. This overlap is considered to be novelty destroying to the present claims.

D9 also contains numerous examples in table 8, which are novelty destroying for the present claims e.g. entry 2,3, 5, 12, ,24, 26 etc. The number of compounds, which are novelty destroying to the present claims which are novelty destroying will depend on the final interpretation of the term "aryl" and "aromatic heterocycle"(see section VIII). Thus e.g.entry 23 of D9 could be novelty destroying for a number of claims.

Differences with subject matter of cited documents

The compounds of the present claims differ from the compounds of D2- D4, D7, D10-D15, D17, D21 through the proviso introduced into claim 1, that $Y\text{-}R^1$ is not hydrogen or alkyl or in the case of claim 56 that $Y\text{-}R^1$ does not include alkyl or hydrogen.

The compounds of the present claims are considered to be a novel selection from those generally disclosed in D5. The compounds of the present claims either differ from those specifically disclosed in D5 through the proviso that $Y\text{-}R^1$ is not alkyl or through the $R^3\text{-}X$ group in claim 56.

The imidazopyridine derivatives of the present claims differ from those of D16 through the number of double bonds. In claim 1 of the present claims it is indicated that the dotted lines represent at least 3, whereas in the compounds of D16, there is only 1 double bond in the tetrahydroimidazopyridine structure.

The compounds of the present claim 1 differ from 1,4,6,7-tetrahydro-1-methyl-2-(methylthio)-alpha-phenyl-5H-imidazo[4,5-c]pyridine-5-ethanol disclosed in D19 through the the number of double bonds in the bicyclic structure, through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7), and the OH group.

The compounds of the present claim 1 differs from that of 5methyl-2-methylthiotriazaindene disclosed in D20 through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7).

It has been assumed that the term "aryl" in claim 1 does not include substituted aryl. In this case compounds 9a and 9b of D22 (page 747) are not novelty destroying to the present claim 1, 48 and 56 (see however section VIII). However, final interpretation will depend on the course of the examination, at the regional stage.

Inventive Step

The closest prior art is considered to be D9, in view of the novelty destroying subject matter that this contains and in that it relates to compounds having antiviral activity.

In view of the disclosures of D9, the skilled person would readily have arrived at the claimed subject matter.

The problem underlying the invention is considered to be the provision of further imidazopyrimidine compounds having a surprising activity compared to the closest prior art.

In the absence of any evidence for such a surprising effect an inventive step cannot be acknowledged.

Furthermore an inventive step cannot however be acknowledged for the present claims for the following reasons:

Reasonable alternatives to the tested examples are allowable. The claims however include modifications of substituents which would not reasonably be expected to solve the problem underlying the invention having regard for common knowledge and biological structure-activity relationships.

The question as to what extent the structure of a chemical compound can be modified without causing major changes in its biological activity is considered to be equally relevant in respect of the question as to whether or not it is credible that all members of a certain group of chemical compounds solve a particular problem.

In the present case the structural differences on passing from the examples to compounds falling in the claims are far greater than the structural differences between compounds falling under the claims and compounds according to the prior art D16 and D19.

For example In the present case -Y-R^1 is limited to halophenyl compounds, whilst Y-R^1 includes variations, which are structurally completely different to this.

VIII

a)The description has not been amended to the new set of claims, leading to an inconsistency between the claims. The present claims are therefore not supported by the description as required by Article 6 EPC.

In this respect the following is to be noted.

-The description refers to the exclusion of various compounds as required on page 28, last line to page 31, line 3. The different scope of exclusion and the fact that they need not be excluded in the description leads to an inconsistency with the claims,

The Applicant has indicated that these disclosures could be removed from the description in due course, if these are not required as a basis for a proviso to distinguish the claim from the prior art.

-There is an inconsistency between the claims and description with respect to the term "aryl", such that the meaning of the claims is not clear from the wording alone.

Thus according to the claims R^3 may be aryl which may be substituted by M-Q.

"Aryl" would normally be understood according to the IUPAC rules as only containing carbon and hydrogen. Since M-Q cannot be e.g. fluorine or CF_3 and these substituents are found on the phenyl group in e.g. example 19 and 20, there is an implication in the light of the description that aryl is intended to encompass "optionally substituted" aryl.
This appears to be supported from the compounds which it is intended to exclude from the invention (see e.g. page 26, lines 30-34).

Similar arguments apply to "aromatic heterocycle".

b)The reasons for the provisos in the claims are only partially explained by the cited prior art and it will become necessary to consider more closely the reasons for the provisos in the present claims.

For example, the proviso may be directed to the exclusion of known prior art compounds which do possess the desired activities.

If in this case, if the said prior art was published before the priority date of the application, it may be necessary to take the prior art into consideration for the assessment of inventive step.

Similarly the reason for the possible exclusion (a) on page 26 and page 29, lines 23 page 29, line34and page 33, line 35

Furthermore it may be necessary to consider why there are differences in the scope of proviso in claims 1 and 2 with respect to the substituent R^3 and is absent in claim 3.

b) The expressions "an amino acid residue" in the claims is considered to be unclear, since the expression gives no indication which part of the molecule of said compounds is intended as substituent. For example the amino acid residue could be such diverse groups as a COOH group, a CH_3 group a HO-benzyl group or HO-benzyl-CH_2-CH(COOH)-NH-. Furthermore it is unclear whether amino acid residue encompasses only the common natural amino acids or whether it is also intended to cover synthetic amino acids or less common amino acids.

If not all of the diverse possibilities are intended e.g. methyl, it is unclear where the bordelines for the definition lie.

The meaning of the terms of a claims should be as far as possible be clear from the wording alone. The expression "an amino acid residue as used in the claims relies on the description for its interpretation".

c) Having regard for claims 1, 2, 3, 48, 56 it appears that these are independent claims. It is however considered that it would be appropriate to cover these by a single independent claim.

d) a lack of clarity arises with certain R^6 substituents, which are unstable. Thus for example OH substituted by -O-alkenylC(=O)OR^{18}.